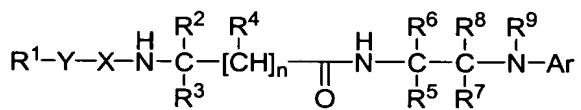


WHAT IS CLAIMED IS:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt or prodrug thereof,

wherein:

R^1 is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with 0-3 R^{1a}, a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated;

each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃ perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃, S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated, and a C₁-C₄ alkyl substituted with 0-2 R¹⁶.

each R^{1b} is independently a member selected from the group consisting of H, OH, F, Cl, acetyl, =O, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃ and OCF₃;

each R^{1c} is independently a member selected from the group consisting of H, OH, F, Cl, =O, C₁-C₆ alkyl substituted with 0-2 R¹⁶, C₁-C₆ alkoxy, CF₃, OCF₃, C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz; phenyl substituted with 0-3 R¹⁵; a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each

31 independently a member selected from the group consisting of N, O and S,
32 wherein said heteroaryl is substituted with 0-2 R¹⁵;
33 R² is a member selected from the group consisting of a phenyl substituted with 0-3
34 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
35 each independently a member selected from the group consisting of N, O and
36 S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted
37 with 0-2 R^{2a}, wherein said C₁-C₆ alkyl optionally contains a heteroatom
38 selected from the group consisting of -O-, -S-, and -S(=O)₂-, a C₂-C₆ alkenyl,
39 a C₂-C₆ alkynyl, a C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹, wherein said C₃-
40 C₇ cycloalkyl optionally contains a heteroatom selected from -O-, -S-, and -
41 S(=O)₂-, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
42 each R^{2a} is independently a member selected from the group consisting of a C₆-C₁₀
43 aryl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic or 8- to 10-
44 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
45 independently a member selected from the group consisting of N, O and S,
46 wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ cycloalkyl
47 substituted with 0-2 R¹⁹, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
48 R³ is a member selected from the group consisting of H and C₁-C₄ alkyl;
49 subscript n is 0 or 1;
50 R⁴ is a member selected from the group consisting of H and C₁-C₆ alkyl;
51 alternatively, R² and R⁴ are taken together to form a C₅-C₇ cycloalkyl substituted with
52 0-2 R¹⁹;
53 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl, C₂-C₆
54 alkenyl, C₂-C₆ alkyne, phenyl substituted with 0-2 R¹⁵; 5- to 6-membered
55 heteroaryl containing 1 to 4 heteroatoms each independently a member
56 selected from the group consisting of N, O and S, wherein said heteroaryl is
57 substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted with 0-2 R¹⁸, wherein said
58 C₁-C₆ alkyl optionally contains a heteroatom selected from the group
59 consisting of -O-, -S-, -S(=O)-, -S(=O)₂- and -NR¹⁷-;
60 Y is a member independently selected from the group consisting of a bond and
61 -(CR²⁰R²¹)_m-W-(CR²²R²³)_p;
62 subscript p is 1 or 2;
63 subscript m is 0 or 1;

64 W is a member independently selected from the group consisting of a bond, -O-, -S-,
65 -S(=O)-, -S(=O)₂- and -NR¹²-;
66 X is selected from the group consisting of -C(=O)-, -OC(=O)-, -NR²⁴C(=O)- and
67 -S(=O)₂-;
68 each of R⁶, R⁷, R⁸ and R⁹ is independently a member selected from the group
69 consisting of H and C₁-C₄ alkyl;
70 alternatively, R⁵ and R⁷ are taken together to form a C₅-C₇ cycloalkyl substituted with
71 0-2 R¹⁹;
72 alternatively, R⁵ and R⁹ are taken together to form a 6-7 membered heterocyclic ring
73 containing 1-2 heteroatoms each independently a member selected from the
74 group consisting of N, O and S;
75 Ar is a member selected from the group consisting of phenyl substituted with 0-3 R²⁹,
76 and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
77 independently a member selected from the group consisting of N, O and S,
78 wherein said heteroaryl is substituted with 0-3 R²⁹;
79 each R¹⁰ is independently a member selected from the group consisting of H, C₃-C₇
80 cycloalkyl, a C₁-C₃ perfluoroalkyl, a C₁-C₄ alkyl substituted with 0-1 R²⁵, a
81 phenyl substituted with 0-3 R¹⁵; a 5- to 6-membered heteroaryl containing 1 to
82 4 heteroatoms each independently a member selected from the group
83 consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵,
84 and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
85 member selected from the group consisting of N, O and S, wherein said
86 heterocycle is substituted with 0-2 R^{1c};
87 each R¹¹ is independently a member selected from the group consisting of H, 'BOC,
88 Cbz, C₃-C₈ cycloalkyl, (C₁-C₆ alkyl)-C(=O)-, (C₁-C₆ alkyl)-S(=O)₂- and a
89 C₁-C₆ alkyl;
90 each of R¹², R¹³ and R¹⁴ is independently a member selected from the group
91 consisting of H and C₁-C₄ alkyl;
92 alternatively, R¹³ and R¹⁴ on the same N atom are taken together to form a C₅-C₇
93 heterocycle containing 1-2 heteroatoms each independently a member selected
94 from the group consisting of N, O and S;
95 each R¹⁵ is independently a member selected from the group consisting of H, OH, F,
96 Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃,

97 -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃
98 perfluoroalkoxy and a C₁-C₆ alkyl;

99 each R¹⁶ is independently a member selected from the group consisting of H, OH,
100 COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃,
101 -S(=O)₂CH₃, C₁-C₆ alkoxy, NR²⁶R²⁷, a phenyl substituted with 0-3 R¹⁵, a 5- to
102 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a
103 member selected from the group consisting of N, O and S, wherein said
104 heteroaryl is substituted with 0-3 R¹⁵, and a C₃-C₈ heterocycle containing 1 to
105 2 heteroatoms each independently a member selected from the group
106 consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵
107 and is saturated or unsaturated;

108 R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl;

109 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
110 Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a
111 C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered
112 heteroaryl containing 1 to 4 heteroatoms each independently a member
113 selected from the group consisting of N, O and S, wherein said heteroaryl is
114 substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms
115 each independently a member selected from the group consisting of N, O and
116 S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or
117 unsaturated; and C₃-C₈ cycloalkyl;

118 each R¹⁹ is independently a member selected from the group consisting of C₁-C₄
119 alkyl, F, Cl and C₁-C₄ alkoxy, CF₃ and OCF₃;

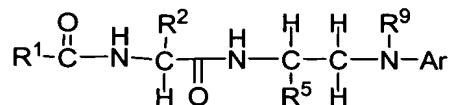
120 alternatively, two R¹⁹ on the same carbon may be combined to form C₃-C₆ cycloalkyl;
121 each of R²⁰, R²¹, R²² and R²³ is independently a member selected from the group
122 consisting of a bond, H, F, OH, C₁-C₄ alkyl, and C₁-C₃ alkylhydroxy;
123 alternatively, R²⁰ and R²¹ or R²² and R²³ are taken together to form a C₃-C₆
124 cycloalkyl;

125 R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;

126 each R²⁵ is independently a member selected from the group consisting of H, C₃-C₇
127 cycloalkyl, a phenyl substituted with 0-3 R¹⁵ and a 5- to 6-membered
128 heteroaryl containing 1 to 4 heteroatoms each independently a member
129 selected from the group consisting of N, O and S, wherein said 5- to 6-
130 membered heteroaryl is substituted with 0-2 R¹⁵;

131 each R²⁶ is independently a member selected from the group consisting of H, C₁-C₄
132 alkyl, (C₁-C₄ alkyl)-C(=O)- and (C₁-C₄ alkyl)-S(=O)₂-;
133 each R²⁷ is independently a member selected from the group consisting of H and
134 C₁-C₄ alkyl;
135 alternatively, R²⁶ and R²⁷ on the same N atom are taken together to form a C₅-C₇
136 heterocycle containing 1-2 heteroatoms each independently a member selected
137 from the group consisting of N, O and S;
138 each R²⁸ is independently a member selected from the group consisting of H, a C₁-C₆
139 alkyl, C₃-C₈ cycloalkyl, a phenyl substituted with 0-3 R¹⁵, a benzyl
140 substituted with 0-2 R¹⁵;
141 each R²⁹ is independently a member selected from the group consisting of H, F, Cl,
142 Br, I, CN, NO₂, OR²⁸, SR²⁸, S(=O)R²⁸, S(=O)₂R²⁸, S(=O)₂NR¹³R¹⁴, NR²⁶R²⁷,
143 acetyl, C(=O)NR¹³R¹⁴, C(=O)OR¹³, C₁-C₆ alkyl, OCHF₂, SCF₃, OCF₃, -
144 C(=NH)NH₂, and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms
145 each independently a member selected from the group consisting of N, O and
146 S;
147 alternatively, two R²⁹ substituted on adjacent atoms may be combined to form a 5 to 6
148 membered heterocyclic fused radical, wherein said 5 to 6 membered
149 heterocyclic fused radical comprise 1 or 2 heteroatom(s) selected from O, S
150 and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted
151 with 0-1 oxo;
152 alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused
153 heterocyclic ring containing 1-2 heteroatom(s) each independently a member
154 selected from the group consisting of N, O and S; wherein said 5 to 7
155 membered fused heterocyclic ring is substituted with 0-2 R¹⁹;
156 each R³⁰ is independently a member selected from the group consisting of H, C₃-C₇
157 cycloalkyl, C₁-C₄ alkyl substituted with 0-1 R²⁵, a phenyl substituted with 0-3
158 R¹⁵, and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
159 independently a member selected from the group consisting of N, O and S,
160 wherein said heteroaryl is substituted with 0-3 R¹⁵; and
161 with the proviso that R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are not all hydrogen.

1 2. The compound of claim 1, according to formula Ia



3 **Ia**

4 wherein:

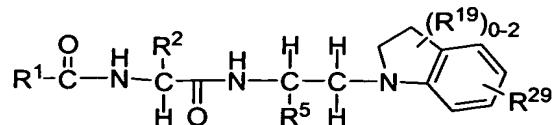
5 R^1 is a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each independently
6 a member selected from the group consisting of N, O and S, wherein said
7 heteroaryl is substituted with 1 R^{1a} ;

8 R^{1a} is independently a member selected from the group consisting of phenyl
9 substituted with 0-2 R^{15} , and a 5- to 6-membered monocyclic heteroaryl
10 containing 1 to 4 heteroatoms each independently a member selected from the
11 group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2
12 R^{15} ;

13 R^2 is a member selected from the group consisting of a phenyl substituted with 0-3
14 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
15 each independently a member selected from the group consisting of N, O and
16 S, wherein said heteroaryl is substituted with 0-2 R^{15} , a $\text{C}_1\text{-}\text{C}_6$ alkyl, a $\text{C}_1\text{-}\text{C}_3$
17 alkyl substituted with 1 R^{2a} , and a $\text{C}_3\text{-}\text{C}_7$ cycloalkyl substituted with 0-2 R^{19} ;
18 each R^{2a} is independently a member selected from the group consisting of a $\text{C}_6\text{-}\text{C}_{10}$
19 aryl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic or 8- to 10-
20 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
21 independently a member selected from the group consisting of N, O and S,
22 wherein said heteroaryl is substituted with 0-3 R^{15} , a $\text{C}_3\text{-}\text{C}_8$ cycloalkyl
23 substituted with 0-2 R^{19} and a $\text{C}_7\text{-}\text{C}_{11}$ bicycloalkyl substituted with 0-2 R^{19} ;
24 and

25 Ar is phenyl substituted with 0-3 R^{29} , or alternatively, R^{29} and R^9 are taken together to
26 form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
27 each independently a member selected from the group consisting of N, O and
28 S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-
29 2 R^{19} .

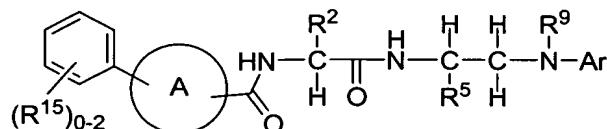
1 3. The compound of claim 2, wherein said compound is of the formula:



1 4. The compound of claim 1, wherein:

2 R¹ is a member selected from the group consisting of phenyl substituted with 0-3 R^{1a},
3 furanyl substituted with 0-3 R^{1a}, C₃-C₆ cycloalkyl substituted with 0-3 R^{1a},
4 indolyl substituted with 0-3 R^{1a}, 5- or 6-membered heterocyclyl substituted
5 with 0-3 R^{1c}, pyridazinyl substituted with 0-3 R^{1a}, imadazolyl substituted with
6 0-3 R^{1a}, thienyl substituted with 0-3 R^{1a}, thiazolyl substituted with 0-3 R^{1a},
7 oxadiazolyl substituted with 0-3 R^{1a}, pyrazolyl substituted with 0-3 R^{1a},
8 isoxazolyl substituted with 0-3 R^{1a}, tetrazolyl substituted with 0-3 R^{1a},
9 oxazolyl substituted with 0-3 R^{1a} and pyridyl substituted with 0-3 R^{1a}.

1 5. The compound of claim 2, according to formula Ib:



3 **Ib**

4 wherein:

5 each R¹⁵, if present, is independently a member selected from the group consisting of
6 OH, F, Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl,
7 -SCH₃, -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃
8 perfluoroalkyl, C₁-C₃ perfluoroalkoxy and a C₁-C₆ alkyl; and

9 A is a 5-membered heteroaryl selected from the group consisting of furanylene,
10 thienylene, thiazolylene, oxadiazolylene, isoxazolylene, tetrazolylene, and
11 oxazolylene.

1 6. The compound of claim 5, wherein:

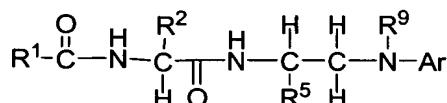
2 R² is a member selected from the group consisting of a C₁-C₂ alkyl substituted with 1
3 R^{2a}, and C₁-C₆ alkyl;

4 each R^{2a} is independently a member selected from the group consisting of a phenyl
5 substituted with 0-3 R¹⁵, and a C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹;

6 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl; a C₁-C₆
7 alkyl substituted with 0-1 R¹⁸, wherein said C₁-C₆ alkyl optionally contains a
8 heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂-
9 and -NR¹⁷-; and

each R¹⁸ is independently a member selected from the group consisting of H, OH, F, Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-C₈ cycloalkyl.

7. The compound of claim 1, according to formula Ia:



Ia

wherein:

R^1 is a member selected from the group consisting of a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein said C₃-C₈ cycloalkyl is saturated or unsaturated and a C₄-C₇ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated;

R^2 is a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C_1 - C_6 alkyl substituted with 0-2 R^{2a} , and a C_3 - C_7 cycloalkyl substituted with 0-2 R^{19} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

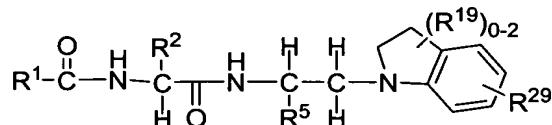
8. The compound of claim 7, wherein:

R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} and C_1 - C_6 alkyl;

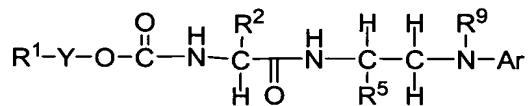
each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R¹⁵, and a C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹:

6 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl; a C₁-C₆
 7 alkyl substituted with 0-1 R¹⁸, wherein said C₁-C₆ alkyl optionally contains a
 8 heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂-
 9 and -NR¹⁷-; and
 10 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
 11 Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3
 12 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
 13 member selected from the group consisting of N, O and S, wherein said
 14 heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-
 15 C₈ cycloalkyl.

1 9. The compound of claim 7, wherein said compound is of the formula:
 2



1 10. The compound of claim 1, according to formula Ic:
 2



Ic

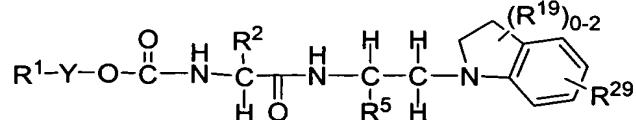
4 wherein:
 5 R¹ is a member selected from the group consisting of tBu, phenyl substituted with 0-2
 6 R¹⁵, a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
 7 independently a member selected from the group consisting of N, O and S,
 8 wherein said heteroaryl is substituted with 0-2 R¹⁵, and a C₄-C₇ heterocycle
 9 containing 1 to 2 heteroatoms each independently a member selected from the
 10 group consisting of N, O and S, wherein said heterocycle is substituted with
 11 0-2 R^{1c};
 12 each R^{1c} is independently a member selected from the group consisting of H, OH, F,
 13 Cl, =O, C₁-C₆ alkyl substituted with 0-2 R¹⁶, a C₁-C₆ alkoxy, CF₃, OCF₃,
 14 C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz, phenyl substituted with 0-3 R¹⁵, and a 5- to
 15 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each

16 independently a member selected from the group consisting of N, O and S,
17 wherein said heteroaryl is substituted with 0-2 R¹⁵;
18 Y is a member independently selected from the group consisting of a bond and
19 -(CR²⁰R²¹)_m-W-(CR²²R²³)_p-, wherein m is 0, W is a bond, and R²²R²³ are both
20 H;
21 R² is a member selected from the group consisting of a phenyl substituted with 0-3
22 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
23 each independently a member selected from the group consisting of N, O and
24 S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₁-C₆ alkyl, a C₁-C₃
25 alkyl substituted with 1 R^{2a}, and a C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹;
26 each R^{2a} is independently a member selected from the group consisting of a C₆-C₁₀
27 aryl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic or 8- to 10-
28 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
29 independently a member selected from the group consisting of N, O and S,
30 wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ cycloalkyl
31 substituted with 0-2 R¹⁹, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
32 and
33 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to
34 form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
35 each independently a member selected from the group consisting of N, O and
36 S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-
37 2 R¹⁹.

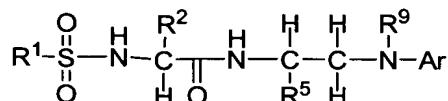
1 11. The compound of claim 10, wherein:
2 R² is a member selected from the group consisting of a C₁-C₂ alkyl substituted with 1
3 R^{2a}, and C₁-C₆ alkyl;
4 each R^{2a} is independently a member selected from the group consisting of a phenyl
5 substituted with 0-3 R¹⁵, and a C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹;
6 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl; a C₁-C₆
7 alkyl substituted with 0-1 R¹⁸, wherein said C₁-C₆ alkyl optionally contains a
8 heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂-
9 and -NR¹⁷-; and
10 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
11 Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3

12 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
13 member selected from the group consisting of N, O and S, wherein said
14 heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-
15 C₈ cycloalkyl.

1 12. The compound of claim 10, wherein said compound is of the formula:



1 13. The compound of claim 1, according to formula Id:



3 **Id**

4 wherein:

5 R¹ is a member selected from the group consisting of methyl, benzyl, C₆-C₁₀ aryl
6 substituted with 0-3 R^{1a}, and a 5- to 6-membered monocyclic or 8- to 10-
7 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
8 independently a member selected from the group consisting of N, O and S,
9 wherein said heteroaryl is substituted with 0-3 R^{1a};

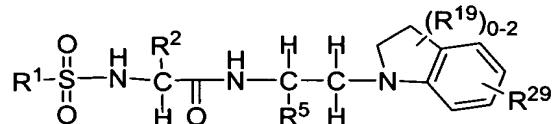
10 each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃
11 perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃,
12 S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴,
13 phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl
14 containing 1 to 4 heteroatoms each independently a member selected from the
15 group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2
16 R¹⁵; and a C₁-C₄ alkyl; and

17 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to
18 form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
19 each independently a member selected from the group consisting of N, O and
20 S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-
21 2 R¹⁹.

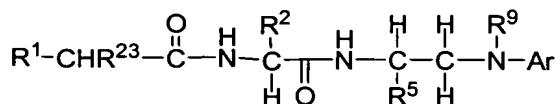
1 **14.** The compound of claim 13, wherein:

2 R² is a member selected from the group consisting of a C₁-C₂ alkyl substituted with 1
3 R^{2a}, and C₁-C₆ alkyl;
4 each R^{2a} is independently a member selected from the group consisting of a phenyl
5 substituted with 0-3 R¹⁵, and a C₃-C₈ cycloalkyl substituted with 0-2 R¹⁹;
6 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl; a C₁-C₆
7 alkyl substituted with 0-1 R¹⁸, wherein said C₁-C₆ alkyl optionally contains a
8 heteroatom selected from the group consisting of -O-, -S-, -S(=O)-, -S(=O)₂-
9 and -NR¹⁷-; and
10 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
11 Cl, CN, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a phenyl substituted with 0-3
12 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
13 member selected from the group consisting of N, O and S, wherein said
14 heterocycle is substituted with 0-2 R¹⁵ and is saturated or unsaturated; and C₃-
15 C₈ cycloalkyl.

1 **15.** The compound of claim 13, wherein said compound is of the formula:



1 **16.** The compound of claim 1, according to formula Ie



3 **Ie**

4 wherein:

5 R¹ is a member selected from the group consisting of a C₆-C₁₀ aryl substituted with
6 0-3 R^{1a}, a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic
7 heteroaryl containing 1 to 4 heteroatoms each independently a member
8 selected from the group consisting of N, O and S, wherein said heteroaryl is
9 substituted with 0-3 R^{1a};

10 each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃
11 perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃,

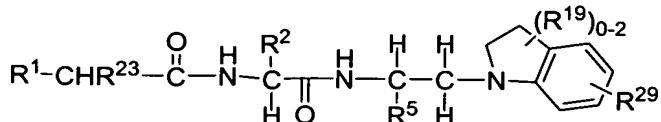
$\text{S}(\text{=O})_2\text{R}^{10}$, $\text{NR}^{11}\text{R}^{12}$, acetyl, $\text{C}(\text{=O})\text{OR}^{13}$, $\text{C}(\text{=O})\text{NR}^{13}\text{R}^{14}$, $\text{S}(\text{=O})_2\text{NR}^{13}\text{R}^{14}$, phenyl substituted with 0-3 R^{15} , a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R^{15} , a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a member selected from the group consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated, and a C₁-C₄ alkyl substituted with 0-2 R^{16} ; and

Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s) each independently a member selected from the group consisting of N, O and S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

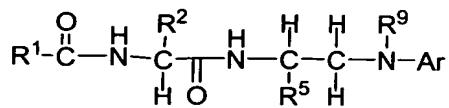
17. The compound of claim 16, wherein:

R^2 is a member selected from the group consisting of a C_1 - C_2 alkyl substituted with 1 R^{2a} , and C_1 - C_6 alkyl; each R^{2a} is independently a member selected from the group consisting of a phenyl substituted with 0-3 R^{15} , and a C_3 - C_8 cycloalkyl substituted with 0-2 R^{19} ; and R^5 is a member selected from the group consisting of H, C_3 - C_7 cycloalkyl; a C_1 - C_6 alkyl, wherein said C_1 - C_6 alkyl optionally contains a heteroatom selected from the group consisting of $-O-$, $-S-$, $-S(=O)-$, $-S(=O)_2-$ and $-NR^{17}-$.

18. The compound of claim 16, wherein said compound is of the formula:



19. The compound of claim 1, according to formula Ia



Ia

wherein:

5 R¹ is a member selected from the group consisting of C₆-C₁₀ aryl substituted with 0-3
6 R^{1a}, and a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic
7 heteroaryl containing 1 to 4 heteroatoms each independently a member
8 selected from the group consisting of N, O and S, wherein said heteroaryl is
9 substituted with 0-3 R^{1a};

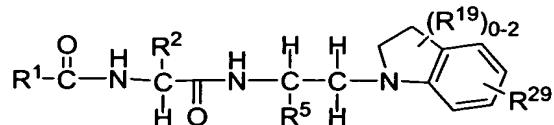
10 each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃
11 perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃,
12 S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴,
13 phenyl substituted with 0-3 R¹⁵; and a C₁-C₄ alkyl substituted with 0-2 R¹⁶;

14 R² is a member selected from the group consisting of a phenyl substituted with 0-3
15 R¹⁵; a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
16 each independently a member selected from the group consisting of N, O and
17 S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₁-C₆ alkyl, a C₁-C₂
18 alkyl substituted with 1R^{2a}, a C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹;

19 each R^{2a} is independently a member selected from the group consisting of a C₆-C₁₀
20 aryl substituted with 0-3 R¹⁵; a 5- to 6-membered monocyclic or 8- to 10-
21 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
22 independently a member selected from the group consisting of N, O and S,
23 wherein said heteroaryl is substituted with 0-3 R¹⁵; a C₃-C₈ cycloalkyl
24 substituted with 0-2 R¹⁹; and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
25 and

26 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to
27 form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
28 each independently a member selected from the group consisting of N, O and
29 S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-
30 2 R¹⁹.

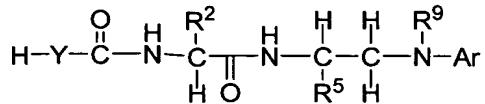
1 20. The compound of claim 19, wherein said compound is of the formula:



1 21. The compound of claim 1, wherein R⁵ and R⁷ are taken together to
2 form a C₅-C₇ cycloalkyl substituted with 0-2 R¹⁹; and

3 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken
4 together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
5 each independently a member selected from the group consisting of N, O and S; wherein said
6 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

1 22. The compound of claim 1, according to formula If



3 If

4 wherein:

5 Y is a member selected from the group consisting of a bond and -

6 (CR²⁰R²¹)_m-W-(CR²²R²³)_p-;

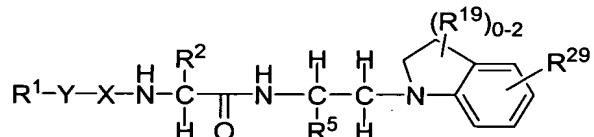
7 subscript p is the integer 1 or 2;

8 subscript m is 0 or 1;

9 W is a oxygen; and

10 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken together to
11 form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
12 each independently a member selected from the group consisting of N, O and
13 S; wherein said 5- to 7-membered fused heterocyclic ring is substituted with 0-
14 2 R¹⁹.

1 23. The compound of claim 1, according to formula Ig:



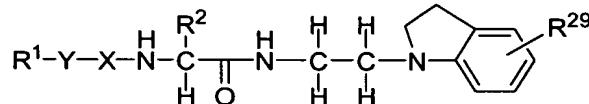
3 Ig

4 wherein:

5 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl, C₂-C₆
6 alkenyl, C₂-C₆ alkyne, phenyl substituted with 0-2 R¹⁵; 5- to 6-membered
7 heteroaryl containing 1 to 4 heteroatoms each independently a member
8 selected from the group consisting of N, O and S, wherein said heteroaryl is
9 substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted with 0-2 R¹⁸, wherein said

10 C₁-C₆ alkyl optionally contains a heteroatom selected from the group
11 consisting of -O-, -S-, -S(=O)-, -S(=O)₂- and -NR¹⁷-.

12
1 **24.** The compound of claim 23, according to formula Ih:

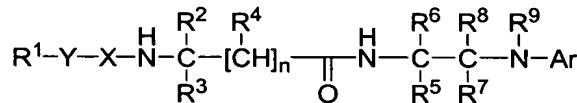


3 **Ih**

1 **25.** The compound of claim 1, wherein R⁹ is H; and
2 Ar is phenyl substituted with 0-3 R²⁹, or alternatively, R²⁹ and R⁹ are taken
3 together to form a 5- to 7-membered fused heterocyclic ring containing 1-2 heteroatom(s)
4 each independently a member selected from the group consisting of N, O and S; wherein said
5 5- to 7-membered fused heterocyclic ring is substituted with 0-2 R¹⁹.

1 **26.** The compound of claim 1, wherein said compound is a member
2 selected from the compounds of Table I.

1 **27.** A pharmaceutical composition comprising: a compound of Formula I:



3 **I**

4 or a pharmaceutically acceptable salt or prodrug thereof,
5 wherein:

6 R¹ is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with
7 0-3 R^{1a}, a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic
8 heteroaryl containing 1 to 4 heteroatoms each independently a member
9 selected from the group consisting of N, O and S, wherein said heteroaryl is
10 substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein
11 said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle
12 containing 1 to 2 heteroatoms each independently a member selected from the
13 group consisting of N, O and S, wherein said heterocycle is substituted with
14 0-2 R^{1c} and is saturated or unsaturated;

15 each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃
16 perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃,

17 S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴,
18 phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl
19 containing 1 to 4 heteroatoms each independently a member selected from the
20 group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2
21 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
22 member selected from the group consisting of N, O and S, wherein said
23 heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated, and a
24 C₁-C₄ alkyl substituted with 0-2 R¹⁶;
25 each R^{1b} is independently a member selected from the group consisting of H, OH, F,
26 Cl, acetyl, =O, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃ and OCF₃;
27 each R^{1c} is independently a member selected from the group consisting of H, OH, F,
28 Cl, =O, C₁-C₆ alkyl substituted with 0-2 R¹⁶, C₁-C₆ alkoxy, CF₃, OCF₃,
29 C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz; phenyl substituted with 0-3 R¹⁵; a 5- to 6-
30 membered monocyclic heteroaryl containing 1 to 4 heteroatoms each
31 independently a member selected from the group consisting of N, O and S,
32 wherein said heteroaryl is substituted with 0-2 R¹⁵;
33 R² is a member selected from the group consisting of a phenyl substituted with 0-3
34 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
35 each independently a member selected from the group consisting of N, O and
36 S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted
37 with 0-2 R^{2a}, wherein said C₁-C₆ alkyl optionally contains a heteroatom
38 selected from the group consisting of -O-, -S-, and -S(=O)₂-, a C₂-C₆ alkenyl,
39 a C₂-C₆ alkynyl, a C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹, wherein said C₃-
40 C₇ cycloalkyl optionally contains a heteroatom selected from -O-, -S-, and -
41 S(=O)₂-, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
42 each R^{2a} is independently a member selected from the group consisting of a C₆-C₁₀
43 aryl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic or 8- to 10-
44 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
45 independently a member selected from the group consisting of N, O and S,
46 wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ cycloalkyl
47 substituted with 0-2 R¹⁹, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
48 R³ is a member selected from the group consisting of H and C₁-C₄ alkyl;
49 subscript n is 0 or 1;
50 R⁴ is a member selected from the group consisting of H and C₁-C₆ alkyl;

51 alternatively, R² and R⁴ are taken together to form a C₅-C₇ cycloalkyl substituted with
52 0-2 R¹⁹;
53 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl, C₂-C₆
54 alkenyl, C₂-C₆ alkyne, phenyl substituted with 0-2 R¹⁵; 5- to 6-membered
55 heteroaryl containing 1 to 4 heteroatoms each independently a member
56 selected from the group consisting of N, O and S, wherein said heteroaryl is
57 substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted with 0-2 R¹⁸, wherein said
58 C₁-C₆ alkyl optionally contains a heteroatom selected from the group
59 consisting of -O-, -S-, -S(=O)-, -S(=O)₂- and -NR¹⁷-;
60 Y is a member independently selected from the group consisting of a bond and
61 -(CR²⁰R²¹)_m-W-(CR²²R²³)_p;
62 subscript p is 1 or 2;
63 subscript m is 0 or 1;
64 W is a member independently selected from the group consisting of a bond, -O-, -S-,
65 -S(=O)-, -S(=O)₂- and -NR¹²-;
66 X is selected from the group consisting of -C(=O)-, -OC(=O)-, -NR²⁴C(=O)- and
67 -S(=O)₂;
68 each of R⁶, R⁷, R⁸ and R⁹ is independently a member selected from the group
69 consisting of H and C₁-C₄ alkyl;
70 alternatively, R⁵ and R⁷ are taken together to form a C₅-C₇ cycloalkyl substituted with
71 0-2 R¹⁹;
72 alternatively, R⁵ and R⁹ are taken together to form a 6-7 membered heterocyclic ring
73 containing 1-2 heteroatoms each independently a member selected from the
74 group consisting of N, O and S;
75 Ar is a member selected from the group consisting of phenyl substituted with 0-3 R²⁹,
76 and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
77 independently a member selected from the group consisting of N, O and S,
78 wherein said heteroaryl is substituted with 0-3 R²⁹;
79 each R¹⁰ is independently a member selected from the group consisting of H, C₃-C₇
80 cycloalkyl, a C₁-C₃ perfluoroalkyl, a C₁-C₄ alkyl substituted with 0-1 R²⁵, a
81 phenyl substituted with 0-3 R¹⁵; a 5- to 6-membered heteroaryl containing 1 to
82 4 heteroatoms each independently a member selected from the group
83 consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵,
84 and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a

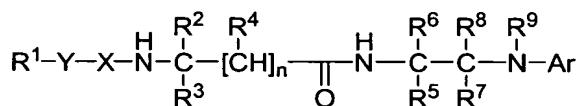
85 member selected from the group consisting of N, O and S, wherein said
86 heterocycle is substituted with 0-2 R^{1c};
87 each R¹¹ is independently a member selected from the group consisting of H, 'BOC,
88 Cbz, C₃-C₈ cycloalkyl, (C₁-C₆ alkyl)-C(=O)-, (C₁-C₆ alkyl)-S(=O)₂- and a
89 C₁-C₆ alkyl;
90 each of R¹², R¹³ and R¹⁴ is independently a member selected from the group
91 consisting of H and C₁-C₄ alkyl;
92 alternatively, R¹³ and R¹⁴ on the same N atom are taken together to form a C₅-C₇
93 heterocycle containing 1-2 heteroatoms each independently a member selected
94 from the group consisting of N, O and S;
95 each R¹⁵ is independently a member selected from the group consisting of H, OH, F,
96 Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃,
97 -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃
98 perfluoroalkoxy and a C₁-C₆ alkyl;
99 each R¹⁶ is independently a member selected from the group consisting of H, OH,
100 COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃,
101 -S(=O)₂CH₃, C₁-C₆ alkoxy, NR²⁶R²⁷, a phenyl substituted with 0-3 R¹⁵, a 5- to
102 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a
103 member selected from the group consisting of N, O and S, wherein said
104 heteroaryl is substituted with 0-3 R¹⁵, and a C₃-C₈ heterocycle containing 1 to
105 2 heteroatoms each independently a member selected from the group
106 consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵
107 and is saturated or unsaturated;
108 R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl;
109 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
110 Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a
111 C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered
112 heteroaryl containing 1 to 4 heteroatoms each independently a member
113 selected from the group consisting of N, O and S, wherein said heteroaryl is
114 substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms
115 each independently a member selected from the group consisting of N, O and
116 S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or
117 unsaturated; and C₃-C₈ cycloalkyl;

118 each R¹⁹ is independently a member selected from the group consisting of C₁-C₄
119 alkyl, F, Cl and C₁-C₄ alkoxy, CF₃ and OCF₃;
120 alternatively, two R¹⁹ on the same carbon may be combined to form C₃-C₆ cycloalkyl;
121 each of R²⁰, R²¹, R²² and R²³ is independently a member selected from the group
122 consisting of a bond, H, F, OH, C₁-C₄ alkyl, and C₁-C₃ alkylhydroxy;
123 alternatively, R²⁰ and R²¹ or R²² and R²³ are taken together to form a C₃-C₆
124 cycloalkyl;
125 R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;
126 each R²⁵ is independently a member selected from the group consisting of H, C₃-C₇
127 cycloalkyl, a phenyl substituted with 0-3 R¹⁵ and a 5- to 6-membered
128 heteroaryl containing 1 to 4 heteroatoms each independently a member
129 selected from the group consisting of N, O and S, wherein said 5- to 6-
130 membered heteroaryl is substituted with 0-2 R¹⁵;
131 each R²⁶ is independently a member selected from the group consisting of H, C₁-C₄
132 alkyl, (C₁-C₄ alkyl)-C(=O)- and (C₁-C₄ alkyl)-S(=O)₂-;
133 each R²⁷ is independently a member selected from the group consisting of H and
134 C₁-C₄ alkyl;
135 alternatively, R²⁶ and R²⁷ on the same N atom are taken together to form a C₅-C₇
136 heterocycle containing 1-2 heteroatoms each independently a member selected
137 from the group consisting of N, O and S;
138 each R²⁸ is independently a member selected from the group consisting of H, a C₁-C₆
139 alkyl, C₃-C₈ cycloalkyl, a phenyl substituted with 0-3 R¹⁵, a benzyl
140 substituted with 0-2 R¹⁵;
141 each R²⁹ is independently a member selected from the group consisting of H, F, Cl,
142 Br, I, CN, NO₂, OR²⁸, SR²⁸, S(=O)R²⁸, S(=O)₂R²⁸, S(=O)₂NR¹³R¹⁴, NR²⁶R²⁷,
143 acetyl, C(=O)NR¹³R¹⁴, C(=O)OR¹³, C₁-C₆ alkyl, OCHF₂, SCF₃, OCF₃, -
144 C(=NH)NH₂, and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms
145 each independently a member selected from the group consisting of N, O and
146 S;
147 alternatively, two R²⁹ substituted on adjacent atoms may be combined to form a 5 to 6
148 membered heterocyclic fused radical, wherein said 5 to 6 membered
149 heterocyclic fused radical comprise 1 or 2 heteroatom(s) selected from O, S
150 and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted
151 with 0-1 oxo;

152 alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused
153 heterocyclic ring containing 1-2 heteroatom(s) each independently a member
154 selected from the group consisting of N, O and S; wherein said 5 to 7
155 membered fused heterocyclic ring is substituted with 0-2 R¹⁹;
156 each R³⁰ is independently a member selected from the group consisting of H, C₃-C₇
157 cycloalkyl, C₁-C₄ alkyl substituted with 0-1 R²⁵, a phenyl substituted with 0-3
158 R¹⁵, and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
159 independently a member selected from the group consisting of N, O and S,
160 wherein said heteroaryl is substituted with 0-3 R¹⁵; with the proviso that R³,
161 R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are not all hydrogen; and
162 an excipient.

1 **28.** The composition of claim 27, wherein said compound is a member
2 selected from the compounds of Table I.

1 **29.** A method of selectively inhibiting cathepsin S activity in a mammal in
2 need thereof, comprising administering to said mammal a therapeutically effective amount of
3 a compound of Formula I:



6 or a pharmaceutically acceptable salt or prodrug thereof,
7 wherein:

8 R¹ is a member selected from the group consisting of H, C₆-C₁₀ aryl substituted with
9 0-3 R^{1a}, a 5- to 6-membered monocyclic or 8- to 10-membered bicyclic
10 heteroaryl containing 1 to 4 heteroatoms each independently a member
11 selected from the group consisting of N, O and S, wherein said heteroaryl is
12 substituted with 0-3 R^{1a}, a C₃-C₈ cycloalkyl substituted with 0-2 R^{1b}, wherein
13 said C₃-C₈ cycloalkyl is saturated or unsaturated; and a C₃-C₈ heterocycle
14 containing 1 to 2 heteroatoms each independently a member selected from the
15 group consisting of N, O and S, wherein said heterocycle is substituted with
16 0-2 R^{1c} and is saturated or unsaturated;

17 each R^{1a} is independently a member selected from the group consisting of H, C₁-C₃
18 perfluoroalkyl, C₃-C₇ cycloalkyl, F, Cl, Br, CN, NO₂, OR¹⁰, SCH₃, S(=O)CH₃,

19 S(=O)₂R¹⁰, NR¹¹R¹², acetyl, C(=O)OR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴,
20 phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic heteroaryl
21 containing 1 to 4 heteroatoms each independently a member selected from the
22 group consisting of N, O and S, wherein said heteroaryl is substituted with 0-2
23 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a
24 member selected from the group consisting of N, O and S, wherein said
25 heterocycle is substituted with 0-2 R^{1c} and is saturated or unsaturated, and a
26 C₁-C₄ alkyl substituted with 0-2 R¹⁶;
27 each R^{1b} is independently a member selected from the group consisting of H, OH, F,
28 Cl, acetyl, =O, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃ and OCF₃;
29 each R^{1c} is independently a member selected from the group consisting of H, OH, F,
30 Cl, =O, C₁-C₆ alkyl substituted with 0-2 R¹⁶, C₁-C₆ alkoxy, CF₃, OCF₃,
31 C(=O)R¹⁰, S(=O)₂R¹⁰, tBoc, Cbz; phenyl substituted with 0-3 R¹⁵; a 5- to 6-
32 membered monocyclic heteroaryl containing 1 to 4 heteroatoms each
33 independently a member selected from the group consisting of N, O and S,
34 wherein said heteroaryl is substituted with 0-2 R¹⁵;
35 R² is a member selected from the group consisting of a phenyl substituted with 0-3
36 R¹⁵, a 5- to 6-membered monocyclic heteroaryl containing 1 to 4 heteroatoms
37 each independently a member selected from the group consisting of N, O and
38 S, wherein said heteroaryl is substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted
39 with 0-2 R^{2a}, wherein said C₁-C₆ alkyl optionally contains a heteroatom
40 selected from the group consisting of -O-, -S-, and -S(=O)₂-, a C₂-C₆ alkenyl,
41 a C₂-C₆ alkynyl, a C₃-C₇ cycloalkyl substituted with 0-2 R¹⁹, wherein said C₃-
42 C₇ cycloalkyl optionally contains a heteroatom selected from -O-, -S-, and -
43 S(=O)₂-, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
44 each R^{2a} is independently a member selected from the group consisting of a C₆-C₁₀
45 aryl substituted with 0-3 R¹⁵, a 5- to 6-membered monocyclic or 8- to 10-
46 membered bicyclic heteroaryl containing 1 to 4 heteroatoms each
47 independently a member selected from the group consisting of N, O and S,
48 wherein said heteroaryl is substituted with 0-3 R¹⁵, a C₃-C₈ cycloalkyl
49 substituted with 0-2 R¹⁹, and a C₇-C₁₁ bicycloalkyl substituted with 0-2 R¹⁹;
50 R³ is a member selected from the group consisting of H and C₁-C₄ alkyl;
51 subscript n is 0 or 1;
52 R⁴ is a member selected from the group consisting of H and C₁-C₆ alkyl;

53 alternatively, R² and R⁴ are taken together to form a C₅-C₇ cycloalkyl substituted with
54 0-2 R¹⁹;
55 R⁵ is a member selected from the group consisting of H, C₃-C₇ cycloalkyl, C₂-C₆
56 alkenyl, C₂-C₆ alkyne, phenyl substituted with 0-2 R¹⁵; 5- to 6-membered
57 heteroaryl containing 1 to 4 heteroatoms each independently a member
58 selected from the group consisting of N, O and S, wherein said heteroaryl is
59 substituted with 0-2 R¹⁵, a C₁-C₆ alkyl substituted with 0-2 R¹⁸, wherein said
60 C₁-C₆ alkyl optionally contains a heteroatom selected from the group
61 consisting of -O-, -S-, -S(=O)-, -S(=O)₂- and -NR¹⁷-;
62 Y is a member independently selected from the group consisting of a bond and
63 -(CR²⁰R²¹)_m-W-(CR²²R²³)_p-;
64 subscript p is 1 or 2;
65 subscript m is 0 or 1;
66 W is a member independently selected from the group consisting of a bond, -O-, -S-,
67 -S(=O)-, -S(=O)₂- and -NR¹²-;
68 X is selected from the group consisting of -C(=O)-, -OC(=O)-, -NR²⁴C(=O)- and
69 -S(=O)₂-;
70 each of R⁶, R⁷, R⁸ and R⁹ is independently a member selected from the group
71 consisting of H and C₁-C₄ alkyl;
72 alternatively, R⁵ and R⁷ are taken together to form a C₅-C₇ cycloalkyl substituted with
73 0-2 R¹⁹;
74 alternatively, R⁵ and R⁹ are taken together to form a 6-7 membered heterocyclic ring
75 containing 1-2 heteroatoms each independently a member selected from the
76 group consisting of N, O and S;
77 Ar is a member selected from the group consisting of phenyl substituted with 0-3 R²⁹,
78 and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
79 independently a member selected from the group consisting of N, O and S,
80 wherein said heteroaryl is substituted with 0-3 R²⁹;
81 each R¹⁰ is independently a member selected from the group consisting of H, C₃-C₇
82 cycloalkyl, a C₁-C₃ perfluoroalkyl, a C₁-C₄ alkyl substituted with 0-1 R²⁵, a
83 phenyl substituted with 0-3 R¹⁵; a 5- to 6-membered heteroaryl containing 1 to
84 4 heteroatoms each independently a member selected from the group
85 consisting of N, O and S, wherein said heteroaryl is substituted with 0-2 R¹⁵,
86 and a C₃-C₈ heterocycle containing 1 to 2 heteroatoms each independently a

87 member selected from the group consisting of N, O and S, wherein said
88 heterocycle is substituted with 0-2 R^{1c};
89 each R¹¹ is independently a member selected from the group consisting of H, 'BOC,
90 Cbz, C₃-C₈ cycloalkyl, (C₁-C₆ alkyl)-C(=O)-, (C₁-C₆ alkyl)-S(=O)₂- and a
91 C₁-C₆ alkyl;
92 each of R¹², R¹³ and R¹⁴ is independently a member selected from the group
93 consisting of H and C₁-C₄ alkyl;
94 alternatively, R¹³ and R¹⁴ on the same N atom are taken together to form a C₅-C₇
95 heterocycle containing 1-2 heteroatoms each independently a member selected
96 from the group consisting of N, O and S;
97 each R¹⁵ is independently a member selected from the group consisting of H, OH, F,
98 Cl, Br, I, CN, NO₂, COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃,
99 -S(=O)CH₃, -S(=O)₂CH₃, NR²⁶R²⁷, C₁-C₆ alkoxy, C₁-C₃ perfluoroalkyl, C₁-C₃
100 perfluoroalkoxy and a C₁-C₆ alkyl;
101 each R¹⁶ is independently a member selected from the group consisting of H, OH,
102 COOR¹³, C(=O)NR¹³R¹⁴, S(=O)₂NR¹³R¹⁴, acetyl, -SCH₃, -S(=O)CH₃,
103 -S(=O)₂CH₃, C₁-C₆ alkoxy, NR²⁶R²⁷, a phenyl substituted with 0-3 R¹⁵, a 5- to
104 6-membered heteroaryl containing 1 to 4 heteroatoms each independently a
105 member selected from the group consisting of N, O and S, wherein said
106 heteroaryl is substituted with 0-3 R¹⁵, and a C₃-C₈ heterocycle containing 1 to
107 2 heteroatoms each independently a member selected from the group
108 consisting of N, O and S, wherein said heterocycle is substituted with 0-2 R¹⁵
109 and is saturated or unsaturated;
110 R¹⁷ is a member selected from the group consisting of H and C₁-C₄ alkyl;
111 each R¹⁸ is independently a member selected from the group consisting of H, OH, F,
112 Cl, CN, NO₂, C(=O)OR³⁰, C(=O)NR¹³R¹⁴, NR¹¹R¹², a C₁-C₃ perfluoroalkyl, a
113 C₁-C₃ perfluoroalkoxy, a phenyl substituted with 0-3 R¹⁵, a 5- to 6-membered
114 heteroaryl containing 1 to 4 heteroatoms each independently a member
115 selected from the group consisting of N, O and S, wherein said heteroaryl is
116 substituted with 0-3 R¹⁵, a C₃-C₈ heterocycle containing 1 to 2 heteroatoms
117 each independently a member selected from the group consisting of N, O and
118 S, wherein said heterocycle is substituted with 0-2 R¹⁵ and is saturated or
119 unsaturated; and C₃-C₈ cycloalkyl;

120 each R¹⁹ is independently a member selected from the group consisting of C₁-C₄
121 alkyl, F, Cl and C₁-C₄ alkoxy, CF₃ and OCF₃;
122 alternatively, two R¹⁹ on the same carbon may be combined to form C₃-C₆ cycloalkyl;
123 each of R²⁰, R²¹, R²² and R²³ is independently a member selected from the group
124 consisting of a bond, H, F, OH, C₁-C₄ alkyl, and C₁-C₃ alkylhydroxy;
125 alternatively, R²⁰ and R²¹ or R²² and R²³ are taken together to form a C₃-C₆
126 cycloalkyl;
127 R²⁴ is a member selected from the group consisting of H and C₁-C₄ alkyl;
128 each R²⁵ is independently a member selected from the group consisting of H, C₃-C₇
129 cycloalkyl, a phenyl substituted with 0-3 R¹⁵ and a 5- to 6-membered
130 heteroaryl containing 1 to 4 heteroatoms each independently a member
131 selected from the group consisting of N, O and S, wherein said 5- to 6-
132 membered heteroaryl is substituted with 0-2 R¹⁵;
133 each R²⁶ is independently a member selected from the group consisting of H, C₁-C₄
134 alkyl, (C₁-C₄ alkyl)-C(=O)- and (C₁-C₄ alkyl)-S(=O)₂-;
135 each R²⁷ is independently a member selected from the group consisting of H and
136 C₁-C₄ alkyl;
137 alternatively, R²⁶ and R²⁷ on the same N atom are taken together to form a C₅-C₇
138 heterocycle containing 1-2 heteroatoms each independently a member selected
139 from the group consisting of N, O and S;
140 each R²⁸ is independently a member selected from the group consisting of H, a C₁-C₆
141 alkyl, C₃-C₈ cycloalkyl, a phenyl substituted with 0-3 R¹⁵, a benzyl
142 substituted with 0-2 R¹⁵;
143 each R²⁹ is independently a member selected from the group consisting of H, F, Cl,
144 Br, I, CN, NO₂, OR²⁸, SR²⁸, S(=O)R²⁸, S(=O)₂R²⁸, S(=O)₂NR¹³R¹⁴, NR²⁶R²⁷,
145 acetyl, C(=O)NR¹³R¹⁴, C(=O)OR¹³, C₁-C₆ alkyl, OCHF₂, SCF₃, OCF₃, -
146 C(=NH)NH₂, and 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms
147 each independently a member selected from the group consisting of N, O and
148 S;
149 alternatively, two R²⁹ substituted on adjacent atoms may be combined to form a 5 to 6
150 membered heterocyclic fused radical, wherein said 5 to 6 membered
151 heterocyclic fused radical comprise 1 or 2 heteroatom(s) selected from O, S
152 and N; wherein said 5 to 6 membered heterocyclic fused radical is substituted
153 with 0-1 oxo;

154 alternatively, R²⁹ and R⁹ are taken together to form a 5- to 7-membered fused
155 heterocyclic ring containing 1-2 heteroatom(s) each independently a member
156 selected from the group consisting of N, O and S; wherein said 5 to 7
157 membered fused heterocyclic ring is substituted with 0-2 R¹⁹;
158 each R³⁰ is independently a member selected from the group consisting of H, C₃-C₇
159 cycloalkyl, C₁-C₄ alkyl substituted with 0-1 R²⁵, a phenyl substituted with 0-3
160 R¹⁵, and a 5- to 6-membered heteroaryl containing 1 to 4 heteroatoms each
161 independently a member selected from the group consisting of N, O and S,
162 wherein said heteroaryl is substituted with 0-3 R¹⁵; and
163 with the proviso that R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are not all hydrogen.

1 30. The method of claim 29, wherein the cathepsin S inhibition constant
2 for a compound of Formula I is less than 10 μM.

1 31. The method of claim 30, wherein the cathepsin S inhibition constant
2 for a compound of Formula I is less than 1.0 μM.

1 32. The method of claim 31, wherein the cathepsin S inhibition constant
2 for a compound of Formula I is less than 0.1 μM.

1 33. The method of claim 29, wherein cathepsin S is selectively inhibited in
2 the presence of at least one other cathepsin.

1 34. The method of claim 33, wherein the inhibition constant of a
2 compound of Formula I for said at least one other cathepsin is at least 10 times greater than a
3 cathepsin S inhibition constant of a compound of Formula I.

1 35. The method of claim 34, wherein the inhibition constant of a
2 compound of Formula I for said at least one other cathepsin is at least 100 times greater than
3 said cathepsin S inhibition constant of a compound of Formula I.

1 36. The method of claim 35, wherein the inhibition constant of a
2 compound of Formula I for said at least one other cathepsin is at least 1000 times greater than
3 said cathepsin S inhibition constant of a compound of Formula I.

1 **37.** The method of claim **29**, wherein said compound is a member selected
2 from the compounds of Table I.